State of the art in mesothelioma

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Introduction

Malignant pleural mesothelioma (MPM) still has a dismal prognosis, and in the next 35 years it is calculated that about one-quarter of a million deaths will occur as a result of this disease in Western Europe [1].

History of asbestos exposure is reported in 70–80% of all cases of mesothelioma and lifetime risk for exposed individuals is up to 20% [2–4]. The two major species of asbestos, crocidolite and chrysotile, are both hazardous. The workers at extraction facilities are at the greatest risk of exposure and development of asbestos-related diseases, but asbestos-cement, insulation and shipyard workers are also at increased risk. Environmental exposure to asbestos can occur as a result of living in areas characterized by natural outcrops of asbestos or asbestos-producing materials, or those close to asbestos-producing or -using plants.

The disease mainly occurs in the fifth to seventh decade of life, and in males more commonly than females (3.6:1).

Molecular biology

The molecular steps leading from asbestos within the parietal pleura to the development of malignant mesothelioma are mostly unknown and certainly numerous. However, it is well known that in normal and premalignant cells, asbestos activates or inactivates a variety of genes, including the epidermal growth factor receptor (EGFR), the insulin receptor and cell cycle regulatory genes such as INK4a/ARF, as well as p16 and NF2 genes [5]. Mutations of the p53 and ras genes, which are frequently mutated in lung carcinomas, are rare in malignant mesotheliomas. In contrast, SV40 Tag sequences are frequently present but are absent in adjacent lung tissues and in lung carcinomas [6, 7]. The biological and clinical significance of this finding is not fully understood and, in addition, some authors believe that the finding is attributable to an underestimation of the contamination by common laboratory plasmids containing SV40 sequences leading to false-positive results [8].

Aberrant methylation of CpG islands in the promoter region of tumor suppressor genes is a frequent mechanism of gene silencing, but in malignant mesothelioma has received scant attention. Methylation of RASSF1A has been linked to malignant mesothelioma and correlates with poor outcome. Aberrant methylation was more commonly observed in the epithelial form of mesothelioma rather than in sarcomatous/ mixed types. Intriguingly, methylation in association with the epithelial form of mesothelioma was found in patients whose tumors showed SV40 Tag sequences. A profile of aberrant methylation may help to distinguish between malignant mesotheliomas and lung adenocarcinomas. For example, methylation of adenomatous polyposis coli (APC) promoter 1A was completely absent in mesotheliomas, although it was the gene most frequently methylated in adenocarcinomas (52%) [9].

Pathology

Histologically, these tumors are composed of fibrous or epithelial elements, or both. The epithelial subtype occasionally causes confusion with peripheral adenocarcinoma of the lung or metastatic carcinomas. Attempts at diagnosis by cytology or needle biopsy of the pleura are often not contributive. Thoracoscopy can be valuable in obtaining adequate tissue specimens for diagnostic purposes. Immunohistochemistry has recently become an essential diagnostic tool to differentiate MPM from other types of cancer. Calretinin and keratin 5/6 are positive for malignant mesothelioma, whereas Ber-EP4, CEA and Leu1 are negative.

Mesothelin is a 40-kDa cell surface differentiation antigen present on normal mesothelial cells and overexpressed in several human tumors, including mesothelioma, ovarian and pancreatic adenocarcinomas [10]. However, mesothelin immunostaining has a low specificity for discriminating between epithelioid mesotheliomas and adenocarcinomas, and its use may be considered in those instances in which the results obtained with the standard panel of immunohistochemical markers used for the diagnosis of mesotheliomas are inconclusive. Because mesothelin is a highly sensitive positive marker for epithelioid mesotheliomas, a negative staining for this marker is an indication against such a diagnosis; however, because of its limited utility, it is not recommended for inclusion in the standard panel of immunohistochemical markers used in the distinction between mesotheliomas and adenocarcinomas.

Clinical presentation

Dull, aching chest pain sometimes accompanied by cough, dyspnea on exertion, fever, malaise and weight loss are the most common presenting symptoms. Dullness to percussion and decreased breathing sounds over the base of the affected lung are the most common physical examination findings.
Pleural and, in a later phase of the clinical history, peritoneal effusions represent major symptomatic problems for at least two-thirds of patients.

Death occurs after a median of 6–9 months as a result of combinations of severe dyspnea, chest wall pain, abdominal distention with ascites, intestinal obstruction, pericardial tamponade, cachexia or pneumonia.

**Diagnosis and staging**

Computed tomography (CT) is usually the primary imaging modality used for disease staging in patients who are being considered for surgery. CT is readily available and provides a significant amount of anatomic information. The results can be used to preclude surgery in patients with obviously unresectable tumors (e.g. diffuse extension of tumor into the chest wall, mediastinum or peritoneum, or distant metastasis). Magnetic resonance imaging (MRI) or positron emission tomography (PET) can then be used as the final preoperative radiological examination to complement CT, particularly in questionable cases. MRI with the use of different pulse sequences and gadolinium-based contrast material can improve the detection of tumor extension, especially to the chest wall and diaphragm. PET is useful for the detection of nodal involvement and occult metastasis. Correlation of all imaging findings is essential in directing exploration to areas of possible invasion and selecting those patients who may benefit from aggressive therapy.

In addition to its role in diagnosis and staging, [18F]fluorodeoxyglucose (FDG) PET has several other advantages in the management of MPM. Patients with MPM may have diffuse pleural thickening but only focal areas of malignancy. Areas of pleural thickening may not necessarily correspond to areas of high metabolic activity, and the most appropriate biopsy site may not be apparent from CT findings. Because FDG PET can provide information about metabolically active areas when findings are correlated with anatomic imaging information, it may be used to help determine the most appropriate biopsy site for obtaining positive results. Moreover, PET may help predict prognosis in patients with MPM. A recent study showed that MPM with higher FDG uptake is associated with significantly shorter survival time. This information may be clinically useful in determining whether to pursue an aggressive therapeutic approach based on the biological features of the tumor.

A histological diagnosis is required once MPM is suspected radiologically. Neither cytological analysis of pleural fluid nor needle aspiration biopsy of a pleural mass is diagnostic, because it is extremely difficult to distinguish between cells of MPM, metastatic adenocarcinoma and severe atypia. In contrast, CT-guided core needle biopsy has been shown to improve diagnostic accuracy. Thoracoscopy or thoracotomy is sometimes necessary, especially when a large core of tissue is needed. Video-assisted thoracoscopic surgery has been shown to have a diagnostic rate of 98%. Thoracoscopic evaluation may also allow more accurate staging of MPM compared with non-invasive methods such as CT and MRI. However, video-assisted thoracoscopic surgery causes postprocedural chest wall seeding in up to one-half of patients. Local postoperative radiotherapy can prevent such seeding. In contrast, seeding caused by imaging-guided biopsy is seen in no more than 22% of patients.

Small amounts of mesothelin can be detected in the blood of some patients with mesothelin-positive cancers and measurement of mesothelin in the blood may be useful for the diagnosis and follow up of some of these patients. In a blinded study, serum samples from 44 patients with histologically proven mesothelioma, 68 matched healthy controls, 40 of whom had been exposed to asbestos, and 160 patients with other inflammatory or malignant lung and pleural diseases were tested for the presence of mesothelin-related proteins. Eighty-four per cent of 44 patients with mesothelioma had raised concentrations of mesothelin-related proteins, compared with three (2%) of 160 patients with other cancers or other inflammatory lung or pleural diseases, and none of 28 controls who had not been exposed to asbestos. Concentrations correlated with tumor size and increased during tumor progression. Seven of the 40 asbestos-exposed individuals had increased serum concentrations of mesothelin-related proteins; three of those seven developed mesothelioma and one developed lung carcinoma within 1–5 years.

None of the 33 asbestos-exposed participants whose serum samples had normal concentrations of mesothelin-related proteins and who were followed up over 8 years developed mesothelioma. Consequently, serum mesothelin could be a useful marker for diagnosis of mesothelioma and to monitor disease progression, and might also prove helpful for screening asbestos-exposed individuals for early evidence of mesothelioma [11].

The new staging system from the International Mesothelioma Interest Group is a tumor–node–metastasis (TNM) system that was initially developed to categorize similar cases into homogeneous prognostic groups to aid evaluation of new treatment options (Tables 1–3) [12, 13]. This staging system emphasizes criteria used to determine the extent of local tumor and lymph node involvement, both of which factors have been shown to be related to the overall survival rate in MPM. With locally advanced tumors, it is important to distinguish between T3 (potentially resectable) and T4 (technically unresectable) disease. This distinction guides the choice of treatment options and implies significant differences in survival. The presence of N3 nodal disease or distant metastasis also precludes surgery. Although surgical staging is often required in patients with potentially resectable lesions, CT, MRI and PET can aid in choosing whether to treat MPM surgically, medically or both.

**Prognosis**

Performance status and weight loss are powerful prognostic factors in mesothelioma. Whereas male sex, older age, and high platelet and leucocyte count have also been validated as poor prognostic factors.
Tumor-related prognostic factors involve the anatomical extent of the tumor, and histological and biological characteristics of the tumor. The oldest, most important biological marker of mesothelioma is the histology, a prognostic factor with a major impact on survival. The survival of patients with an epithelial type of mesothelioma might be twice the survival of patients with a mixed or sarcomatoid type. This difference is apparent in both surgical series and in patients who received a non-surgical treatment. The invasive growth pattern of sarcomatoid mesothelioma hampers surgical procedures and major surgery is therefore not recommended in these patients.

Prognostic scoring systems have been proposed by the European Organization for Research and Treatment of Cancer (EORTC) [14] and by the Cancer and Leukaemia Group B (CALGB) [15]. These systems were derived from statistical analysis of large series of patients within chemotherapy trials. Two EORTC risk groups were identified after multivariate analysis of prognostic variables from 204 patients entered into five consecutive trials. The factors included in the model were: white blood cell count >8.3 x 10^9/l, Eastern Cooperative Oncology Group performance status ≥1, sarcomatoid mesothelioma hampers surgical procedures and major surgery is therefore not recommended in these patients.

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**Table 1. Tumor descriptors for malignant pleural mesothelioma**

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Region involved</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>T1a</td>
<td>Limited to the ipsilateral parietal pleura, including the mediastinal and diaphragmatic pleurae</td>
<td>No involvement of the visceral pleura</td>
</tr>
<tr>
<td>T1b</td>
<td>Ipsilateral parietal pleura, including the mediastinal and diaphragmatic pleurae</td>
<td>Scattered tumor foci that also involve the visceral pleura</td>
</tr>
<tr>
<td>T2</td>
<td>Each ipsilateral pleural surface</td>
<td>At least one of the following: (i) involvement of the diaphragmatic muscle; or (ii) a confluent visceral pleural tumor (including fissures) or tumor extension from the visceral pleura into the underlying pulmonary parenchyma</td>
</tr>
<tr>
<td>T3</td>
<td>Locally advanced but potentially resected tumor (each ipsilateral pleural surface)</td>
<td>At least one of the following: (i) involvement of the endo-thoracic fascia; (ii) extension into mediastinal fat; (iii) a solitary, completely resectable focus of tumor that extends into the soft tissues of the chest wall; or (iv) non-transmural involvement of the pericardium</td>
</tr>
<tr>
<td>T4</td>
<td>Locally advanced, technically unresectable tumor (each ipsilateral pleural surface)</td>
<td>At least one of the following: (i) diffuse tumor extension or multiple tumor foci in the chest wall with or without associated rib destruction; (ii) direct transdiaphragmatic extension to the peritoneum; (iii) direct extension to the contralateral pleura; (iv) direct extension to the mediastinal organs; (v) direct extension to the spine; or (vi) extension to the internal surface of the pericardium with or without pericardial effusion or involvement of the myocardium</td>
</tr>
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**Table 2. Node and metastasis descriptors for malignant pleural mesothelioma**

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes not assessable</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases in ipsilateral bronchopulmonary or hilar lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in subcarinal or ipsilateral mediastinal lymph nodes, including ipsilateral internal mammary lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastases in contralateral mediastinal, contralateral internal mammary, and ipsilateral or contralateral supraclavicular lymph nodes</td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastases not assessable</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

**Table 3. Tumor–node–metastasis stage classification for malignant pleural mesothelioma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Node</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Ib</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>Any T3</td>
<td>Any N1 or N2</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T4</td>
<td>Any N3</td>
<td>Any M1</td>
</tr>
</tbody>
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Treatment

Many new therapeutic modalities for MPM have been investigated, either as single treatment approach or as combined therapy. To date, there is no cure for MPM and consensus is lacking on its best management. Physicians are faced with a huge volume of conflicting literature, advocating diverse options from palliation only to aggressive multimodality therapy.

Age and co-morbidity often prohibit aggressive therapeutic options in the individual patient. The median time lag between asbestos exposure and development of MPM is >30 years, hence most patients are relatively old at presentation. About 20% also have co-existing pulmonary fibrosis from asbestosis. In addition, many patients are smokers with limited cardiot- espiratory reserve.

The number of MPM patients treated by surgery is still rather small. Various surgical procedures may be possible in selected patients, providing long-term survival without cure. Although some patients with early-stage disease experience long-term survival with aggressive treatment approaches including extensive surgery, adjuvant chemotherapy and radiotherapy, it remains unclear whether overall survival has been significantly altered by the different treatment modalities or by combinations of modalities. Extrapleural pneumonectomy in selected patients with early-stage disease may improve recurrence-free survival, but its impact on overall survival is unknown. Pleurectomy and decortication can provide palliative benefit from symptomatic effusions, discomfort caused by tumor burden and pain caused by invasive tumor. Operative mortality from pleurectomy/decortication is <2%, while mortality from extrapleural pneumonectomy has been reported to range from 6% to 30%.

For patients undergoing surgery the main prognostic factors are male sex, high platelet count, and large preoperative and postcytoreduction tumor volumes [16].

The use of radiotherapy in pleural mesothelioma has been shown to alleviate pain in the majority of patients treated. However, the duration of symptom control is short-lived [17].

Chemotherapy has been disappointing. EORTC examined several cytotoxic drugs as mitoxantrone, epirubicin, etoposide and paclitaxel, with no objective responses and median survivals ranging from 6.7 to 9 months [14].

Single-agent and combination chemotherapy have been evaluated in single and combined modality studies. Until recently, the most studied agent was doxorubicin, which has produced partial responses in ~15–20% of treated patients. Some combination chemotherapy regimens have been reported to have higher response rates in small phase II trials; however, the toxicity reported is also higher, and there is no evidence that combination regimens result in longer survival or longer control of symptoms [18].

In MPM, gemcitabine and cisplatin, given as single agents, have shown response rates ranging from 7% to 14%, and in vitro studies have suggested a synergic interaction between these two compounds. A pivotal single institutional study reported a response rate of 48% with this two-drug regimen [19]. However, a larger phase II study by the same authors [20] and additional phase II studies [21] have documented a significantly lower level of efficacy.

Recently, pemetrexed has shown promising activity in MPM. Pemetrexed is a folate antimetabolite that primarily inhibits thymidylate synthase (TS). The penaglutamate form of pemetrexed is the predominant intracellular form, and is >60-fold more potent in its inhibition of TS. A phase I study of pemetrexed plus carboplatin in 27 patients with stage III and IV showed a response rate of 32% according to the strict criteria of response assessment by measuring the thickness of pleural tumor at three separate levels on transverse cuts on each thoracic CT scan. Median time to progression was 10 months and median survival 15 months [22].

In a large phase III study, the combination of cisplatin and pemetrexed was associated with significantly improved survival time and with overall greater antitumor activity compared with cisplatin alone. The regimen was well tolerated, particularly in patients who received low-dose folic acid and vitamin B12. Vitamin supplementation reduced toxicity with no apparent adverse affect on efficacy [23].

Pharmacogenetic tests can contribute to elucidate which patients can respond to a specific chemotheraphy combination. Overexpression of TS mRNA could correlate with resistance to pemetrexed, and overexpression of nucleotide excision repair genes such as ERCCI mRNA correlates with resistance to cisplatin or carboplatin.

Another antimetabolite, raltitrexed, was combined with oxaliplatin and tested in 70 (15 pretreated and 55 chemotherapy-naive) patients with diffuse MPM. In the overall study population, 14 patients (20%) had a partial response and 32 patients (46%) had stable disease. The symptomatic response rates were as follows: shortness of breath, 36%; pain, 30%; activity, 23%; appetite, 21%; and asthenia, 20%. Median time to disease progression was 18 weeks and overall 1-year survival was 26%. The most common adverse events were asthenia, nausea/vomiting and paresthesia, and no treatment-related deaths were reported [24]. An EORTC phase III trial compared cisplatin plus raltitrexed versus cisplatin in 229 patients with advanced MPM. Preliminary data indicate a non-statistically significant superiority of the combination in terms of median survival time, but more mature data are needed [25].

Ranpirnase (Onconase®; p30 protein) is a novel RNAse derived from frogs’ eggs. As ranpirnase treatment was associated with encouraging survival in certain subsets of patients and showed an acceptable toxicity in a phase II trial [26], a phase III study was designed. This study randomized 154 patients to receive either doxorubicin or ranpirnase. The median and 1-year survival rates were similar in both arms: 7.7 versus 8.2 months, and 30.7% versus 32% (ranpirnase versus doxorubicin). The authors assumed that these disappointing data were caused by an excess of poor prognosis patients in the ranpirnase versus the doxorubicin arm [27].

Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) appear to be important...
autocrine growth factors for mesothelioma, and different strategies aimed at blocking the autocrine loops have been recently explored [28, 29]. Three VEGF inhibitors, SU4166, bevacizumab, and thalidomide, are currently evaluated in phase II studies in mesothelioma patients. Imatinib mesilate and PTK787, two PDGF-associated tyrosine kinase inhibitors, are also under clinical investigation.

In addition, ~70% of malignant mesotheliomas have high level of expression of EGFR, and a subset of cell lines derived from MPM patients express both EGFR and transforming growth factor-α, suggesting an autocrine role even for EGFR. However, two pivotal studies testing EGFR-tyrosine kinase inhibitors have shown only limited level of activity [30, 31].

Chemical or thoracoscopic (either medical or video-assisted) pleurodesis is useful in preventing fluid re-accumulation and should be performed as early as possible.

Intrapleural administration of drugs or photodynamic therapy allows direct delivery to the pleural surfaces, but therapy administered in this manner usually fails to adequately penetrate the tumor and underlying tissues.

With disease progression, trapped lung can occur with tumor involvement of the visceral pleura. Once trapped lung syndrome develops, pleurodesis is unlikely to be successful. Small catheter drainage may provide an alternative to inpatient pleurodesis, especially for patients with advanced disease, but carries the risk of tumor metastasis along the catheter tract. Pleuroperitoneal shunting is not recommended because of the potential risk of enhancing malignant spread to the peritoneal cavity.

If dyspnea does not improve after adequate management of the pleural effusion, supplementary oxygen and opioids may help to reduce breathlessness.

References


